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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,403	08/12/1999	WILLIAM R. ARATHOON	P1099C1	2534
23552	7590	09/10/2004	EXAMINER	
MERCHANT & GOULD PC P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903			HOLLERAN, ANNE L	
			ART UNIT	PAPER NUMBER
			1642	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/373,403	ARATHOON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 May 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 30-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10/03/2003</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The amendment filed May 13, 2004 is acknowledged. Claims 50-55 are added.
Claims 30-55 are pending and examined on the merits.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections/Objections Withdrawn:

3. The objection to the specification because the newly provided pages of the tables have margins that are too small to accommodate the whole punching is withdrawn in view of the amendment filed 5/13/2004.
4. The objection to claim 48 because it appears to contain a typographical error where "C_H3 domain" is incorrectly set forth as "C,3 domain" is withdrawn in view of the amendment.
5. The rejection of claims 43-49 under 35 U.S.C. 103(a) as being unpatentable over Ridgway (Protein Engineering, 9: 617-621, 1996; cited in the IDS), Carter (U.S. Patent 5,807,706; issued September 15, 1998; effective filing date of March 1, 1995) or Carter (WO 96/27011; published September 1996; cited in the IDS), in view of Kostelney (Journal of Immunology, 148: 1547-1553, 1992; cited in the IDS), and further in view of Vaughan (supra) is withdrawn in view of applicants' persuasive arguments. Although Kostelney teaches the

Art Unit: 1642

problem of heavy/light chain miss-parings in methods of making bispecific antibodies, Kostelney fails to provide a suggestion to look to Vaughan, which happens to teach scFv constructs that bind different antigens but have light chains in common, because Kostelney solves the problem using another method. Thus, there is no suggestion provided in the prior art to combine the references.

6. The rejection of claims 30-42 under 35 U.S.C. 112, first paragraph, because the specification fails to reasonably provide enablement commensurate with the scope of the claimed invention is withdrawn in view of the amendment to the claims.

Claim Rejections/Objections Maintained:

7. The provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-51 of copending Application No. 09/863,693 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject matter, a terminal disclaimer may be filed if appropriate.

8. The provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47-63 of copending Application No. 09/520,130 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject matter, a terminal disclaimer may be filed if appropriate.

9. The provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 10/143,437 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject matter, a terminal disclaimer may be filed if appropriate.

10. The rejection of claims 30-42 under 35 U.S.C. 112, first paragraph, on the grounds that the applicants were not in possession of the claimed inventions at the time of filing, because the disclosure of the specification fails to adequately describe the claimed genus of compounds to be made in the claimed methods and encoded by the nucleic acids of the claimed host cells is maintained. New grounds of rejection are presented. This is a new matter rejection.

The basis for this rejection is that the amendment to the specification to recite claims drawn to methods of making multispecific antibodies comprising binding domains, where the binding domains are made up of a heavy and light chain, and where the light chain is not the same for all of the binding domains is not supported by the specification. Therefore, the recitation of claim 30 “where the light chains of the first and additional polypeptides each have three CDR regions, and have at least 98% sequence identity and only differ from one another at amino acid positions outside of the CDR regions” is not supported by the specification as originally filed. The specification teaches methods of making multispecific antibodies, where the each of the binding domains comprises a “common light chain”. The specification defines “common light chain” or “common amino acid sequence of the light chain” on page 21, and as an amino acid sequence of *the* light chain in the multispecific antibody. There does not appear to

be any contemplation of multispecific antibodies comprising more than one light chain (i.e., there appears to be only the contemplation that the same light chain is used for all of the binding domains present in the multispecific antibody). Even a difference of 1 amino acid between the two light chains results in a bispecific antibody having two different light chains, and there is no support in the specification that demonstrates that applicant conceived of a method of making multispecific antibodies having two different light chains. Other instances in the specification that indicate that applicant conceived of methods of making bispecific antibodies where all of the binding domains comprise a light chain having the same sequence is found at page 10, lines 20-21; page 10, line 29 – page 11, line 1; page 12, line 15-line 24; page 13, lines 6-13; page 16, line 1-15; page 56, lines 13-29; page 95, lines 25-28; and page 103, lines 5-8.

Applicants have pointed to passages (page 97-98) in the specification and assert that these passages provide support for the concept of multispecific antibodies comprising light chains where the light chains have at least 98% sequence identity to each other and only differ from one another at amino acid positions outside the CDR regions. However, this teaching of the specification appears to be directed to the process of selecting a light chain that will be used in the process of making a multispecific antibody (i.e. selecting a common light chain). The teachings on page 97 of the specification do not provide support for bispecific antibodies having two different light chains, but instead are directed to a process for identifying one light chain that may be useful in making a bispecific antibody. Applicant is reminded that the description requirement is severable from the enablement requirement.

New Grounds of Rejection:

11. Claims 41-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 is indefinite because of the recitation “host cell comprising a nucleic acid encoding the multispecific antibody of claim 30. Claim 30 is drawn to a method using a host cell that comprises at least 2 nucleic acids (“a nucleic acid encoding the first polypeptide and a nucleic acid encoding at least one additional polypeptide”). Amendment of claim 41 to replace the phrase “a nucleic acid” with “the nucleic acids” will obviate this rejection.

Claim 43 is indefinite because the recitation “the binding region of each first and additional polypeptide of the multispecific antibody” lacks antecedent basis in the claim.

Claim 43 is also indefinite because it appears that it is drawn to a method of making a multispecific antibody that comprises a first and at least a second polypeptide, where the first polypeptide comprises an altered amino acid residue, which is an amino acid from the at least second polypeptide, that specifically interacts with the same amino acid that is also present in the at least second polypeptide. This is not clear because claim 45 reads on alterations so that one polypeptide has an amino acid that creates a protuberance and the other polypeptide has an amino acid that creates a cavity. Therefore, the two amino acids should be different.

Claim 44 is indefinite because it appears to be a recitation of limitations already present in claim 43.

Claim 45 is indefinite because it appears to be outside the scope of claim 43.

Art Unit: 1642

Claim 50 is indefinite because of the phrase “the common variable light chain of the first and additional polypeptides *have* at least...”. The verb “have” is plural, but the subject “the common variable light chain” is singular.

Claim 50 is also indefinite because “the common variable light chain” does not have antecedent basis in the claim. Amendment to “the common light chain”, which has antecedent basis from “a common light chain”, would overcome this rejection.

Claim 50 is indefinite because of the phrase “variable light chain”. Do applicants intend “variable domain of a light chain”? The phrase “variable light chain” is not art-recognized.

Claim 50 is indefinite because the phrase “the variable light chain”, where “the variable light chain” is part of the binding domains of the first and additional polypeptides, does not have antecedent basis in the claim.

12. Claims 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated host cells comprising nucleic acids encoding the multispecific antibody of claim 30, does not reasonably provide enablement for host cells comprised within a transgenic animal or an animal or human being having been treated by gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 41 and 42 are drawn to host cells comprising nucleotide sequences that encodes a multispecific antibody. The specification teaches that a host cell may be an isolated host cell in culture or may be a host cell within a host animal (page 72, line 13-14). Therefore, claims 41

Art Unit: 1642

and 42 encompass transgenic animal hosts and animal hosts that have been treated with gene therapy.

(A)As drawn to gene therapy.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the protein's compartmentalization or fate within the cell are primary considerations regarding effective therapy. Eck state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues

Art Unit: 1642

pointed out by Verma or Eck. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B) as drawn to a transgenic animal

The specification does not provide guidance in the making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predictable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287, see bridging pages 272-273) and expression is heavily dependent on the site of integration in the host genome, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make the instant recombinant polynucleotides and cells within a transgenic animal.

Amendment of the claims to recite "isolated host cell" would overcome this rejection.

13. Claims 50 and 53-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The basis for this rejection is that the addition of claims 50 and 53-55, which are drawn to methods of making multispecific antibodies where the first and additional polypeptides each

Art Unit: 1642

comprise a binding domain, the binding domains comprising a heavy chain and a common light chain, where the common light chain of the first and additional polypeptides has at least 98% sequence identity to each light chain of a first antibody and at least one additional antibody is not supported in the specification. The passages pointed to by applicant include the finding that the differences between the sequences of the compared light chains occurs outside the CDRs. This limitation is not present in the claims and the lack of this limitation is a broadening of scope that was not originally contemplated when the application was filed.

Conclusion

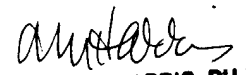
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
September 4, 2004


ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER
9/7/2004